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Health-related quality of life predicts outcomes but is not affected by peritoneal clearance: The ADEMEX trial

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Background. We hypothesized that increasing small solute clearance in peritoneal dialysis (PD) would lead to improvements in patient health-related quality of life (HRQOL).

Methods. Patients were randomized to a control group [standard 4×2L continuous ambulatory peritoneal dialysis (CAPD)] and an intervention group (CAPD with a target creatinine clearance ≥60L/week/1.73m^2). The Kidney Disease Quality of Life Short Form was obtained at baseline and at 6, 12, and 24 months. Physical (PCS), mental (MCS), and kidney disease component summary (KDCS) scores were computed.

Results. The two groups were comparable at baseline with respect to HRQOL. Baseline variables highly predictive of better QOL included absence of diabetes, younger age, higher starting GFR, and serum albumin. Baseline values of QOL were highly predictive of survival and hospitalizations.

An unadjusted comparison revealed that patients in the intervention group had significantly higher PCS and KDCS scores at six months. However, there were no significant differences between the intervention and control patients at 12 or 24 months. When similar analyses were carried out adjusting for different patterns of patient dropout, there were no significant differences between the two groups at any time point in terms of PCS, MCS, and KDCS scores.

Conclusion. We found no evidence of a long-term benefit in HRQOL of CAPD patients by increasing peritoneal small-solute clearances when HRQOL parameters were adjusted for patient dropout. Measures of HRQOL have a significant predictive value for patient survival and hospitalizations.

Patients' perception of their well-being and patient-reported outcomes are becoming an integral part of current evaluations of the human cost of chronic illnesses and the assessment of the impact of therapeutic interventions [1–8]. These trends have been reflected in the field of renal replacement therapies (RRT) by the string of publications, both cross-sectional [7, 9–24] and longitudinal [3, 4, 12, 25, 26], examining the determinants of health-related quality of life (HRQOL) in patients with end-stage renal disease (ESRD) and the predictive value of findings using a variety of evaluative instruments [15, 23, 26–28]. Indeed, measures of HRQOL have not only become popular investigative tools, but have been used in an effort to define and alter models of healthcare delivery [2, 29, 30].

In patients on hemodialysis (HD), several factors have been identified to influence HRQOL, including gender [13, 14], race [9, 10, 19, 24, 31], socioeconomic status [10, 20, 26, 32], body mass index [16], comorbidity [9, 10, 14, 20, 32–36], nutritional status [14, 16, 20, 32], anemia [14, 16, 34, 35], and evidence of inflammation [16]. In HD patients, dialysis dose has not been found to affect HRQOL measures [14, 16, 20, 32], while contradictory findings have been reported for age [16, 20, 32, 34, 35] and duration of dialysis [14, 16]. Further, in patients on HD, measures of HRQOL have been found to be strong independent predictors of hospitalization and increased risk of death [16, 23, 24, 37], but not of compliance with dialytic therapy [38]. HRQOL in patients on HD has been observed to decline over time [34].

Determinants of HRQOL have been less studied in patients on peritoneal dialysis (PD), and all studies to date were in small patient groups. Nevertheless, in PD patients, the following factors have been identified to influence HRQOL measures: gender [25], race [25], socioeconomic status [25], body mass index [25], comorbidity [25, 34, 35], anemia [1], nutritional status [25, 35], and residual renal function [34, 35]. In PD patients, dialysis dose has not been found to affect HRQOL measures [25, 34, 39], nor have indices of inflammation [25]. Further, in patients on PD, measures of HRQOL have been found to be strong independent predictors of hospitalization and increased risk of death [25, 37]. HRQOL in patients on PD, like in patients on HD, has been observed to decline over time [25, 34].

Key words: peritoneal dialysis, adequacy, small solute clearance, quality of life, informative censoring.

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To date, there have been very few large-scale studies that have investigated the determinants of HRQOL in patients on PD or the impact of prospective increments in small solute clearances on various patient outcomes, including HRQOL. While a number of smaller-scale studies have examined the association between small solute clearance and patient HRQOL, these studies were observational in nature and studied small patient groups [25, 34, 39].

While most studies have failed to show a survival benefit of increasing peritoneal small solute clearances beyond a range currently practiced [40–45], it has been speculated that increasing peritoneal clearances may improve other important outcome measures, such as patient HRQOL. A randomized, prospective, controlled clinical trial is required to substantiate the presence or absence of a potential HRQOL effect from a high peritoneal clearance. In this paper, we summarize results from the ADEMEX trial, a large-scale randomized, controlled trial designed specifically to investigate the effects of increasing peritoneal small solute clearance on various patient outcomes, including quality of life [45].

METHODS

Patients and clinical trial design

We conducted a prospective randomized controlled clinical trial called ADEMEX (ADEquacy of peritoneal dialysis in MEXico), which examined the effect of increasing peritoneal dialysis small solute clearances on select patient outcomes in individuals with ESRD treated with continuous ambulatory peritoneal dialysis (CAPD). The local clinical research committees of all participating centers approved the study protocol, and all study subjects gave written informed consent. Patients were recruited from 24 dialysis centers in 14 Mexican cities. The study enrolled 965 patients on CAPD between June 1998 and May 1999. Patients were randomized into either a control group ($N = 484$ patients receiving a standard dose of 4×2L CAPD) or an intervention group ($N = 481$ patients receiving a modified CAPD prescription aimed at achieving a creatinine clearance $\geq$60L/week/1.73m^2). By design, the study was terminated in May 2001, when the last enrolled patient completed two years of follow-up. A complete description of the study design, patient characteristics, and more can be found in a previous publication [45].

KDQOL questionnaire

While the primary purpose of the study was to compare patient survival between standard and high-dose peritoneal dialysis, it was also hypothesized that an increase in peritoneal small solute clearance may lead to improved patient quality of life. To that end, quality of life was assessed at baseline, and approximately at 6, 12, and 24 months thereafter (a window of $\pm$ 2 months) using the Kidney Disease Quality of Life (KDQOL) questionnaire, short form, version 1.3 (KDQOL-SF^{TM}), from the Rand Corporation [46] which has been validated in a Mexican population [47]. The KDQOL questionnaire is a validated quality-of-life instrument that combines the generic SF-36 instrument with a kidney disease-specific instrument. The SF-36 instrument measures eight dimensions or domains of functioning and well-being on a 100-point scale (the higher the scale the better the patient's HRQOL). The eight domains are: (*1*) physical functioning; (*2*) role limitations caused by physical problems; (*3*) pain; (*4*) general health; (*5*) energy/fatigue; (*6*) emotional well-being; (*7*) role limitations caused by emotional problems; and (*8*) social function. In addition to individual comparisons across all eight SF-36 domains, results from the SF-36 instrument were further summarized into a physical composite summary (PCS) score and a mental composite summary (MCS) score using the RAND scoring algorithm [46]. The PCS aggregates items from physical functioning, role-physical, bodily pain, general health, vitality, and social functioning. The MCS aggregates items from role-emotional, mental health, and also includes elements of general health, vitality, and social functioning. In the general population, the mean for each summary scale is 50 points, with a standard deviation of 10 points.

The disease-specific component of the KDQOL instrument measures eleven domains, also on a 100-point scale, related to kidney disease [26]. These domains are: (*1*) burden of kidney disease; (*2*) cognitive function; (*3*) dialysis staff encouragement; (*4*) effects of kidney disease; (*5*) patient satisfaction; (*6*) quality of social interaction; (*7*) sexual function; (*8*) sleep; (*9*) social support; (*10*) symptom problem; and (*11*) work status. A kidney disease component summary (KDCS) score, also on 100-point scale, was computed per Mapes et al [23].

The KDQOL was administered to patients at visits scheduled at approximately 6, 12, and 24 months following randomization. At each scheduled visit, patients were asked to fill out the KDQOL questionnaire with all patients, both literate and illiterate, assisted by a nurse participating in the study. Studies in other dialysis populations have shown that interviewer-administered or assisted surveys avoid selection bias [48].

Statistical methods

Pearson's chi-square test and Fisher exact test were used to compare discrete baseline patient characteristics (e.g., gender, diabetes, comorbidity), while the Student *t* test and Wilcoxon rank-sum test were used to compare continuous variables at baseline (e.g., age, serum chemistries, etc.). Life table techniques in combination with a log-rank test, as well as Cox proportional hazards

regression, were used to compare patient and technique survival [49, 50]. Poisson regression with overdispersion was used to compare hospital admission rates and hospitalization days.

Preliminary comparisons in the mean HRQOL scores between control and intervention groups were carried out using least squares analysis of variance (ANOVA) in conjunction with robust generalized estimating equations (GEE) for repeated measurements [51, 52]. Under this initial analysis, unadjusted mean scores at each period of follow-up were compared based on an ANOVA assuming independent observations with homogeneous variances. The ANOVA assumption of equal variances was evaluated, and found to hold for both the composite scores and individual HRQOL scores. Since repeated HRQOL measurements within individuals tend to be correlated, comparisons of the unadjusted means were carried out using robust standard errors computed under the GEE approach [51, 52].

In order for the unadjusted ANOVA to provide a valid comparison of HRQOL between control and intervention patients, the assumption is made that missing data resulting from patient dropout or withdrawal prior to completion of the study (e.g., dropout due to death, change in therapy, transplant, etc.) is missing completely at random (MCAR). This occurs when the probability of dropout (i.e., withdrawal) from the study is independent of both observed and unobserved values of the outcome of interest, namely, HRQOL. In most studies of HRQOL, this assumption is seldom met [53]. To safeguard against violations to this assumption, a pattern-mixture repeated measures analysis of covariance (ANCOVA) was carried out in which HRQOL scores were compared between control and intervention patients adjusting for different patterns of patient dropout [54, 55]. There are four patterns of missing data resulting from patient drop out. They are: HRQOL measured at baseline followed by dropout prior to month 6; HRQOL measured at baseline and month 6 prior to dropout; HRQOL measured at baseline, month 6, and month 12 prior to dropout; HRQOL measured at baseline, month 6, month 12, and month 24 (patient completed the study).

A pattern-mixture repeated measures ANCOVA was carried in which these four groups (i.e., dropout patterns) were included as indicator covariates in an overall ANCOVA model in order that unbiased estimates of mean HRQOL scores can be calculated and compared between control and intervention patients [54, 55]. Average HRQOL scores were calculated as least squares means averaged across the different patterns of missing data using centered covariates [55]. Correlations were accounted for by assuming a compound symmetric covariance structure. To protect against misspecification of the covariance structure, all comparisons were carried out using robust standard errors [51, 52]. Finally, preliminary analyses revealed a low correlation between serum albumin and nPNA (correlation = 0.18), indicating that these two variables could be included as joint covariates in the various models without jeopardizing the interpretation of results due to statistical multicollinearity.

RESULTS

Patient characteristics and baseline HRQOL findings

Of the 965 patients who participated in the ADEMEX trial, 923 had quality-of-life measurements at baseline (460 control, 463 intervention), and are the subject of this report and all subsequent results and analysis contained herein. Patients in the two groups were similar at baseline with respect to various demographic measurements, ESRD etiology, dialysis parameters at baseline, select serum chemistries, and quality-of-life component summary scores (Tables 1 and 2). Similarly, there were no differences between the control and intervention groups with respect to baseline comorbid conditions (data not shown). By study design, patients in the intervention group had significantly greater peritoneal clearances compared to those in the control group. Specifically, over the course of the study, mean peritoneal creatinine clearances (mean ± 1 standard error) averaged 46 ± .45 L/week/1.73m^2 for the control group and 57 ± .48 L/week/1.73m^2 for the intervention group ($P < 0.001$). Likewise, the mean peritoneal Kt/V values averaged 1.62 ± 0.02 for control patients and 2.13 ± 0.02 for intervention patients ($P < 0.001$). There was no significant difference in the time averaged GFR between the two groups (intervention-control mean difference of -0.20 ± 0.11 mL/min, $P =$ NS), nor were there differences in nPNA and serum albumin values over the course of the study.

Impact of enhanced clearance on HRQOL

Unadjusted mean HRQOL scores at baseline (time = 0) and at 6, 12, and 24 months thereafter are summarized in Table 2. There is some evidence of an early benefit in HRQOL at 6 months for patients in the intervention group. Specifically, of the 19 HRQOL domains (11 KD domains and eight SF-36 domains), a significant difference favoring the intervention group at six months was observed in four of the domains (burden of kidney disease, effects of kidney disease, sexual function, and symptom problem), while patients in the control group had a significantly higher HRQOL score at six months in two of the domains (cognitive function and quality of social interaction) (Table 2). There were no statistically significant differences in mean HRQOL scores for any of the eight SF-36 domains at any point during the study, although there was evidence of moderate improvement in

Table 1. Characteristics of the total study population at baseline and the two subgroups at randomization

Factor	Total			Control			Intervention		
	N	Mean/%	SD	*N*	Mean/%	SD	*N*	Mean/%	SD
Demographics									
Age	923	47.09	13.86	460	47.54	14.07	463	46.65	13.64
BSA	923	1.69	0.19	460	1.68	0.18	463	1.70	0.19
Female	390	42.25%		186	40.43%		204	44.06%	
Male	533	57.74%		274	59.56%		259	55.93%	
DM	392	42.47%		197	42.82%		195	42.11%	
ESRD etiology									
Diabetes	379	41.06%		191	41.52%		188	40.60%	
Glomerulonephritis	57	6.17%		28	6.08%		29	6.26%	
Hypertension	101	10.94%		52	11.30%		49	10.58%	
Obstructive uropathy	24	2.60%		15	3.26%		9	1.94%	
Other/unknown	320	34.66%		155	33.69%		165	35.63%	
Dialysis parameters									
Incident patients	388	42.03%		187	40.65%		201	43.41%	
Prevalent patients	535	57.96%		273	59.34%		262	56.58%	
Prior time on dialysis *months*	866	13.83	24.99	430	14.58	26.15	436	13.08	23.80
GFR *mL/min*	919	1.58	2.17	457	1.61	2.30	462	1.55	2.03
Basal GFR <1 mL/min	506	55.05%		259	56.67%		247	53.46%	
Basal GFR >1 mL/min	413	44.95%		198	43.32%		215	46.53%	
Peritoneal CrCl *L/wk/1.73*	923	44.61	8.71	460	44.70	8.98	463	44.51	8.44
Peritoneal Kt/V	910	1.59	0.38	452	1.58	0.37	458	1.59	0.39
Laboratory parameters									
Serum creatinine *mg/dL*	923	10.75	3.80	460	10.80	4.02	463	10.69	3.57
Serum urea nitrogen *mg/dL*	910	52.51	17.53	452	52.79	17.80	458	52.24	17.27
Hematocrit%	764	28.56	5.98	382	28.85	6.16	382	28.27	5.80
Hemoglobin *g/dL*	864	9.08	1.92	431	9.19	1.96	433	8.97	1.89
Serum albumin *g/dL*	898	2.92	0.64	441	2.89	0.64	457	2.94	0.63
nPNA *g/kg/day*	901	0.80	0.22	445	0.81	0.23	456	0.80	0.21

Abbreviations are: DM, diabetes mellitus; nPNA, normalized protein nitrogen appearance rate. The control and intervention groups were identical for all measures.

Table 2. Baseline and follow up HRQOL measures in the two subgroups at randomization

Instrument	Domain	Treatment							
		Control follow-up *months*				Intervention follow-up *months*			
		0 Mean	6 Mean	12 Mean	24 Mean	0 Mean	6 Mean	12 Mean	24 Mean
N		460	342	269	117	463	212	153	72
KD QOL	Kidney Disease Component Summary	53.4	53.1[a]	53.7	53.6	53.9	54.9	54.0	54.8
	Symptom problem	76.2	77.8[b]	79.0	78.5	76.8	81.2	79.4	79.2
	Dialysis staff encouragement	95.5[a]	95.7	96.2	97.3	97.3	96.7	97.4	94.5
	Patient satisfaction	24.5	24.2	24.1	24.9	25.0	25.0	24.7	24.6
	Effects of kidney disease	65.2	64.9[b]	67.3	66.9	65.7	69.4	66.7	69.0
	Burden of kidney disease	41.8	44.2[a]	47.3	45.0	43.1	50.2	51.4	52.7
	Work status	34.7	32.3	32.5	33.0	32.0	33.3	35.3	40.8
	Cognitive function	28.6	27.1[b]	25.0	26.7	27.8	22.1	22.0	23.2
	Quality of social interaction	24.5	24.3[b]	22.4	24.7	22.5	19.1	20.4	21.7
	Sexual function	56.2	50.5[b]	57.7	46.4	61.3	67.7	50.6	63.0
	Sleep	64.3	65.0	66.1	63.7	65.0	67.6	66.7	67.9
	Social support	76.3	76.3	74.3	75.4	76.6	78.6	76.9	71.2
SF-36	Mental Component Summary	48.3	50.0	49.2	47.3	48.9	50.1	50.5	50.5
	Physical Component Summary	37.3	36.8[a]	38.3	38.1	37.7	38.8	37.8	37.6
	Physical functioning	52.2	50.6	51.0	52.7	54.0	53.5	52.6	52.8
	Role-physical	38.8	43.6	46.3	42.9	39.4	46.1	43.8	46.5
	Pain	68.8	68.8	72.9	70.3	69.3	73.3	72.6	67.7
	General health	47.2	47.5	48.2	47.2	49.2	51.6	50.1	50.7
	Emotional well-being	67.1	69.0	67.2	66.6	68.4	69.8	69.8	70.9
	Role-emotional	63.5	70.3	68.5	60.7	65.4	68.4	72.0	70.0
	Social function	67.9	70.4	70.5	70.4	68.5	72.6	72.8	69.9
	Energy/fatigue	53.2	54.2	54.5	50.6	54.9	57.0	54.3	57.5

[a] $P < 0.05$ vs. intervention.
[b] $P < 0.01$ vs. intervention

the physical component summary score at six months for the intervention group.

The preceding results assume mean scores for patients still active in the study at 24 months are representative of all patients participating in the study, including those patients who started but did not complete the study because of dropout due to death, transfer to another modality, or transplant. Examination of patient status at end of study, however, reveals that only 42% of patients completed the minimum planned follow-up of 24 months and, hence, had completed the HRQOL evaluation at that time point, the balance having dropped out because of death (22.1% control; 21.1% intervention), transplant (7.6% control; 5.4% intervention), transfer to hemodialysis (9.78% control; 13.4% intervention), loss to follow-up (9.78% control; 7.77% intervention), or other. Since patient HRQOL generally declines immediately prior to an adverse event, such as death or transfer to another modality, it is important to conduct some sort of sensitivity analysis to determine if patient dropout is informative with respect to mean changes in HRQOL. For example, it is reasonable to assume that patients who drop out before a scheduled visit have a worse HRQOL than those who complete their HRQOL questionnaire at the time of their scheduled visit. If this is true, then unadjusted comparisons are likely to be biased.

In this study, although the overall rate of dropout is similar for both groups, there were differences in reasons for dropout by treatment group. In particular, there was a higher percentage of dropout among patients in the intervention group compared to the control group for reasons of discomfort (intervention: 3.7%, control: 0.2%, $P < 0.001$); hernia (intervention: 2.6%, control: 0.9%, $P < 0.05$); and peritonitis (intervention: 9.7%, control: 5.7%, $P < 0.05$). Conversely, 24 of 460 (5.2%) control patients dropped out due to uremia compared to none for the intervention group ($P < 0.001$). Given the substantial dropout that occurred over the course of the study and the close relationship that may exist between quality of life and adverse events associated with patient withdrawal, it is very possible that unadjusted mean HRQOL scores observed over the course of the study unfairly reflect a relatively healthier population of patients left behind. Such selection bias caused by patient dropout can result in HRQOL data that are informatively censored, which, in turn, can result in biased estimates of mean HRQOL over time.

Illustrations of the effects of informative censoring are depicted in Figures 1 to 3, where mean PCS, MCS, and KDCS scores are plotted against time according to the different patterns of missing data resulting from patient dropout (i.e., according to the patient's last measured HRQOL). For example, as illustrated in Figure 1, those patients who drop out before 12 months had a significantly different mean PCS profile compared to both

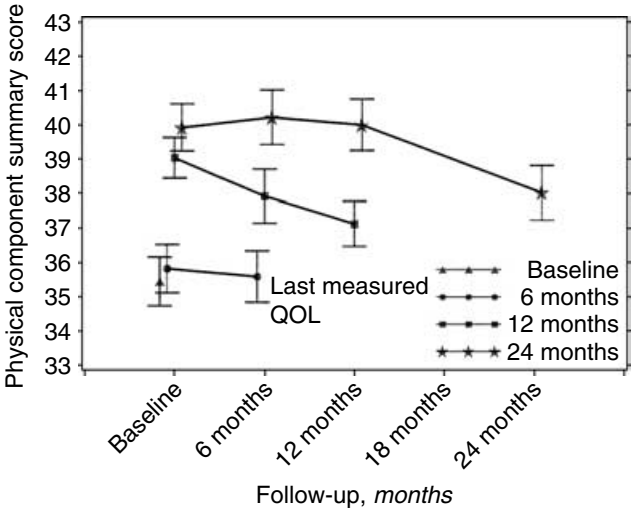

Fig. 1. Physical component summary scores (PCS) (mean ± 1 SE) by pattern of patient dropout (or last measured QOL).

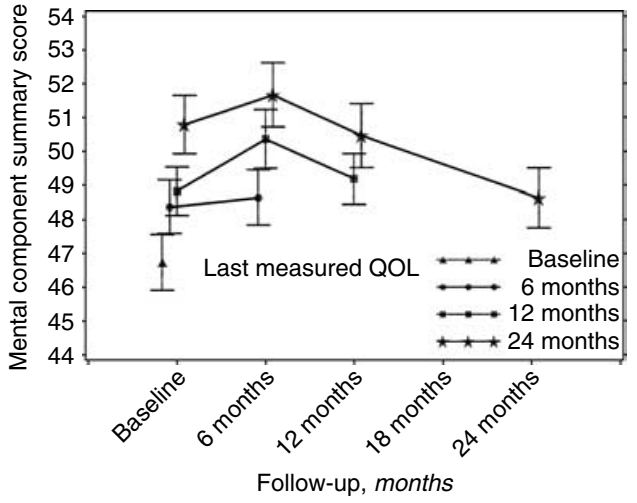

Fig. 2. Mental component summary scores (MCS) (mean ± 1 SE) by pattern of patient dropout (or last measured QOL).

those who last completed their HRQOL assessment at 12 months ($P < 0.001$) and to those that last completed their HRQOL assessment at 24 months ($P < 0.001$). Likewise, patients who completed their 12-month HRQOL assessment but not their 24-month assessment had lower mean PCS scores than those who completed their 24-month HRQOL assessment ($P = 0.0246$). Similar results are seen with the MCS scores (Fig. 2) and KDCS scores (Fig. 3).

In order to more accurately estimate and compare mean HRQOL scores between intervention and control patients, and to compare mean changes from baseline between the two groups, we included the four different patterns of missing data resulting from patient dropout as covariates within a repeated measures ANCOVA model. The results show that there is little or no difference in

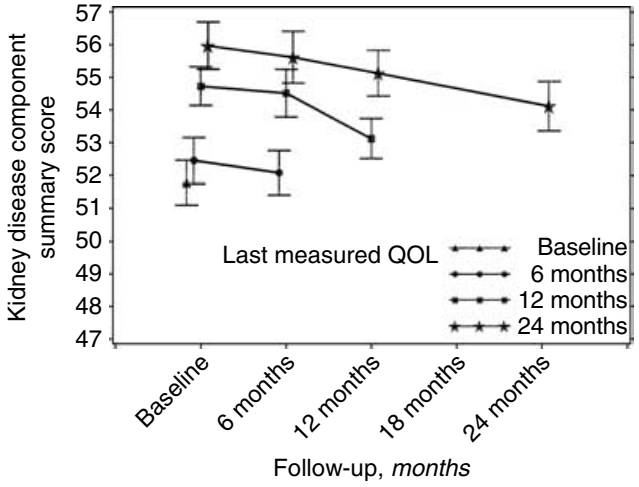

Fig. 3. Kidney disease component summary scores (KDCS) (mean ± 1 SE) by pattern of patient dropout (or last measured QOL).

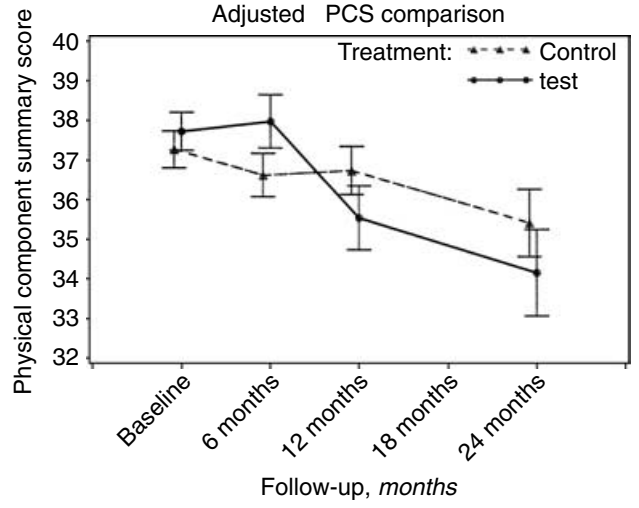

Fig. 4. Comparison of adjusted physical component summary scores (PCS) temporal profiles in the control and intervention groups. No differences between the two groups were observed at any time point. Mean ± 1 SE.

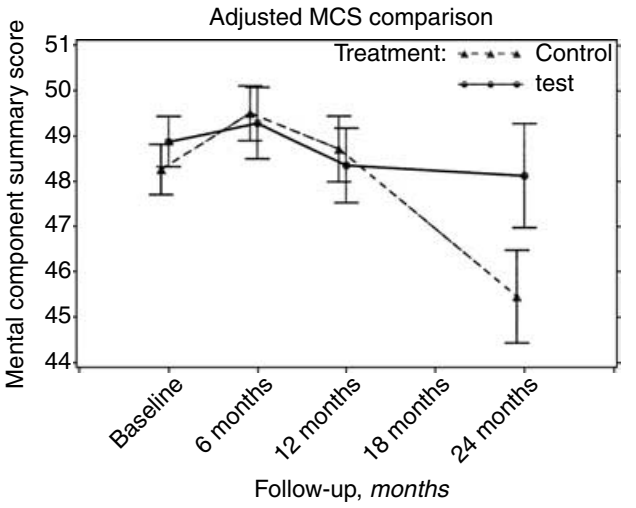

Fig. 5. Comparison of adjusted mental component summary scores (MCS) temporal profiles in the control and intervention groups. No differences between the two groups were observed at any time point. Mean ± 1 SE.

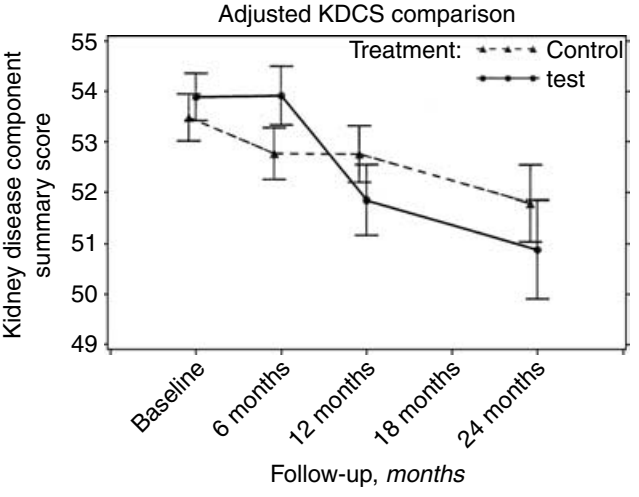

Fig. 6. Comparison of adjusted kidney disease component summary scores (KDCS) temporal profiles in the control and intervention groups. No differences between the two groups were observed at any time point. Mean ± 1 SE.

patient quality of life between patients receiving standard 4×2 L CAPD versus those receiving a modified CAPD prescription aimed at achieving a peritoneal creatinine clearance ≥60 L/week/1.73m^2. These results are portrayed graphically in Figures 4 to 6.

The effect of ignoring patient dropout in the analysis is illustrated in Figure 7, which compares adjusted and unadjusted mean physical component summary scores over the course of the study for both control and intervention patients. For both groups, the unadjusted (raw) mean PCS scores tend to be inflated over time because patients who remain in the study longer tend to be healthier than those who dropout. When adjusted for the different patterns of patient dropout, the mean PCS scores are lower than the raw scores, suggesting that analyses that ignore missing HRQOL scores due to patient dropout may yield overly optimistic values. Similar trends are seen with respect to mean MCS and mean KDCS scores (data not shown). In the majority of cases, trends over time within both the control and intervention groups showed a general decline in HRQOL over a 24-month time frame, although there were trends for a small increase in HRQOL six months' post baseline. There were no statistically significant differences in mean changes from baseline between control and intervention patients for either the physical, mental, or kidney disease component summary scores.

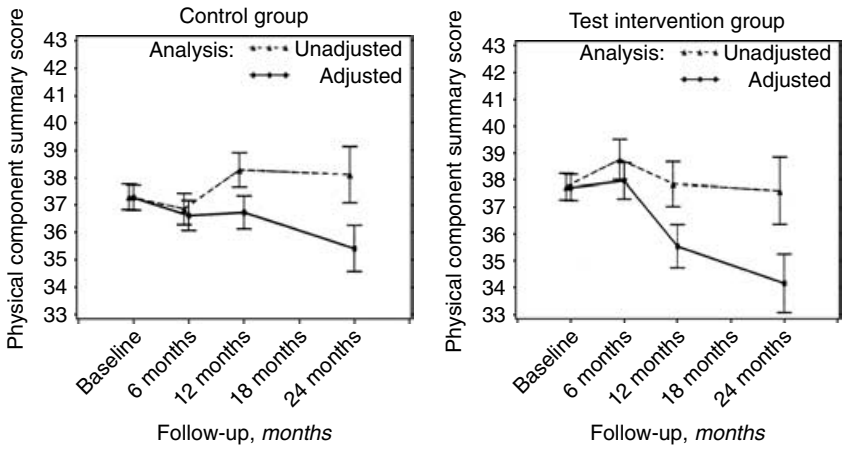

Fig. 7. Adjusted versus unadjusted physical component summary scores over time in the two groups. Use of unadjusted values would have obscured the temporal decline in HRQOL in both groups.

Table 3. Effect of baseline age, serum albumin, presence of diabetes, starting GFR, and gender on patient quality of life

Instrument	Domain	Covariate				
		Age	Albumin	Diabetes	GFR	Female
KD QOL	Kidney Disease Component Summary	−0.138[c]	0.922	−5.719[c]	0.506[c]	0.154
	Symptom problem	−0.119	1.508	−7.256[c]	0.799[b]	−3.017[b]
	Dialysis staff encouragement	−0.004	0.391	0.043	0.096	−0.418
	Patient satisfaction	−0.101[b]	1.826[b]	−6.366[c]	0.223	−0.990
	Effects of kidney disease	−0.109	0.982	−8.343[c]	1.019[c]	1.726
	Burden of kidney disease	−0.249[b]	0.722	−11.23[c]	0.574	4.151
	Work status	−0.496[c]	3.048	−13.11[c]	1.739[b]	−1.324
	Cognitive function	0.104	−1.242	4.715[a]	−0.641	1.326
	Quality of social interaction	0.003	−1.173	3.951[a]	−0.249	−1.429
	Sexual function	−0.515	2.317	−18.79[c]	1.620[a]	4.053
	Sleep	−0.241[c]	0.794	−7.804[c]	1.098[b]	−0.222
	Social support	0.038	−0.131	−4.356[b]	−0.078	1.535
SF-36	Mental Component Summary	−0.002	1.231	−4.527[c]	0.462[b]	−1.083
	Physical Component Summary	−0.135[c]	1.799[b]	−5.159[c]	0.585[c]	−1.242
	Physical functioning	−0.409[c]	5.737[c]	−18.62[c]	1.534[c]	−5.442[b]
	Role-physical	−0.294[a]	6.342[b]	−13.86[c]	1.798[b]	0.892
	Pain	−0.248[c]	2.966[a]	−8.767[c]	0.947[a]	−5.720[c]
	General health	−0.077	2.793[a]	−8.814[c]	1.177[b]	−1.410
	Emotional well-being	−0.062	2.921[a]	−9.946[c]	0.910[b]	−3.776[a]
	Role-emotional	−0.156	4.834[a]	−14.74[c]	1.225[a]	−2.841
	Social function	−0.093	3.448[a]	−10.52[c]	1.050[b]	−0.360
	Energy/fatigue	−0.162[a]	3.715[b]	−13.11[c]	1.246[b]	−3.287[a]

Value is the change in value of the mean QOL score per 1 unit increase in the value of the covariate.
[a] $P < 0.05$.
[b] $P < 0.01$.
[c] $P < 0.001$.

Correlates of baseline HRQOL

In order to investigate what effects gender, age, diabetes, prior time on dialysis (months), and baseline values of GFR (mL/min), serum albumin (g/dL), hematocrit, and nPNA (g/kg/day) have on patient HRQOL, we fit the data to a repeated measures ANCOVA model. The results, summarized in Table 3, indicate that older age, lower serum albumin, presence of diabetes, lower starting GFR, and female gender are all significantly associated with decreased quality of life. For the most part, hematocrit, prior months on dialysis, and nPNA levels at baseline were not predictive of HRQOL, although higher hematocrit levels were associated with a higher HRQOL in terms of burden of kidney disease (value = 0.484, $P < 0.05$) and social support (value = 0.251, $P < 0.05$), while prior months on dialysis was associated with higher HRQOL in terms of work status (value = 0.151, $P < 0.01$) and role physical (value = 1.107, $P < 0.05$). Protein intake as measured via nPNA was associated with better HRQOL in terms of patient satisfaction (value = 4.908, $P < 0.01$), physical functioning (value = 12.638, $P < 0.01$), and role-emotional (value = 13.252, $P < 0.05$).

Predictive value of baseline HRQOL

We compared overall patient survival between intervention and control groups using baseline HRQOL

Table 4. Associations between baseline characteristics and mortality rates

Effect	RR (95% CI)[1]	RR (95% CI)[2]
Treatment (control)	1.10 (0.86,1.40) NS	1.14 (0.89,1.46) NS
Gender (male)	1.21 (0.95, 1.55) NS	1.29 (1.002, 1.65)[a]
Age (per 10 year ?)	1.14 (1.01, 1.28)	1.15 (1.03, 1.29)[a]
DM (non-DM)	1.75 (1.31, 2.34)[c]	1.71 (1.27, 2.30)[c]
Serum albumin (per 0.1 g/dL ?)	0.94 (0.92, 0.96)[c]	0.94 (0.93, 0.96)[c]
nPNA (per 0.1 g/kg/day ?)	0.92 (0.86, 0.98)[b]	0.91 (0.86, 0.97)[a]
PCS (per 5-point scale ?)	1.13 (1.06, 1.21)[c]	
MCS (per 5-point scale ?)	1.07 (1.02, 1.12)[b]	
KDCS (per 5-point scale ?)		1.14 (1.07, 1.23)[c]

NS, Not Significant, A Cox regression analysis was run comparing treatment groups adjusted for gender, age, diabetes, and baseline values of albumin, nPNA, and QOL (as measured by PCS, MCS. and KDCS scores). Adjusted for PCS and MCS as these two scores are approximately uncorrelated. Adjusted for KDCS independent of PCS and MCS (with which KDCS is correlated).

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

measures as covariates. The results, shown in Table 4, clearly demonstrate the impact low starting HRQOL has on subsequent patient outcomes. In particular, even after adjusting for age, diabetes, nPNA, and serum albumin, there was a strong and significant association between baseline physical, mental, and kidney disease component summary scores and mortality, as assessed using a Cox proportional hazards model. Because PCS and MCS scores are constructed to be approximately uncorrelated, they were included in one Cox model, while KDCS scores were included in a second Cox model because of the high correlation that exists between KDCS scores and both PCS and MCS scores. Similarly, identical analysis revealed that even after adjusting for age, diabetes, nPNA, and serum albumin, there was a strong and significant association between baseline physical, mental, and kidney disease component summary scores and hospitalization rates (Table 5) and hospitalization days (Table 5) (as assessed using Poisson regression). Again, because PCS and MCS scores are constructed to be approximately uncorrelated, they were included in one model, while KDCS scores were included in a second model.

The impact of baseline HRQOL parameters on survival is further illustrated in Figure 8A to C. In this analysis, the population was divided into subgroups based on the median for each composite summary score. Patients with values above the median for PCS (Fig. 8A), MCS (Fig. 8B), or KDCS (Fig. 8C) had a better survival than patients with values below the median for these composite summary scores, irrespective of the study arm (control vs. intervention) to which they were randomized.

Identical analysis revealed that after adjusting for age, diabetes, nPNA, and serum albumin, there was no association between baseline physical, mental, and kidney disease component summary scores and technique survival, as assessed using a Cox proportional hazards model.

Table 5. Associations between baseline characteristics and hospitalization rates and hospitalization days

Effect	RR[c] (95% CI)[a]	RR[c] (95% CI)[b]
Hospitalization rate		
Treatment (control)	1.13 (0.95,1.33)NS	1.10 (0.92,1.31)NS
Gender (male)	1.15 (0.97, 1.36) NS	1.19 (0.99, 1.42) NS
Age (per 10 year ↑)	0.92 (0.85, 0.99)[d]	0.91 (0.85, 0.99)[d]
DM (non-DM)	1.38 (1.13, 1.70)[e]	1.47 (1.19, 1.83)[f]
Serum albumin (per 0.1 g/Dl ↑)	0.97 (0.96, 0.98)[f]	0.97 (0.95, 0.98)[f]
nPNA (per 0.1 g/kg/day ↑)	0.97 (0.93, 1.01) NS	0.97 (0.93, 1.02) NS
PCS (per 5-point scale ↓)	1.07 (1.03, 1.12)[e]	
MCS (per 5-point scale ↓)	1.04 (1.003, 1.08)[d]	
KDCS (per 5-point scale ↓)		1.05 (1.00, 1.10)[d]
Hospitalization days		
Treatment (control)	1.10 (0.89,1.37) NS	1.07 (0.86,1.34) NS
Gender (male)	1.11 (0.89, 1.39) NS	1.15 (0.92, 1.45) NS
Age (per 10 year ↑)	1.00 (0.91, 1.11) NS	1.00 (0.90, 1.10) NS
DM (non-DM)	1.48 (1.14, 1.92)[e]	1.55 (1.18, 2.04)[e]
Serum albumin (per 0.1 g/dL ↑)	0.97 (0.95, 0.99)[e]	0.97 (0.95, 0.99)[e]
nPNA (per 0.1 g/kg/day ↑)	0.98 (0.92, 1.03) NS	0.97 (0.92, 1.03) NS
PCS (per 5-point scale ↓)	1.06 (0.99, 1.12) NS	
MCS (per 5-point scale ↓)	1.07 (1.03, 1.12)[e]	
KDCS (per 5-point scale ↓)		1.08 (1.02, 1.15)[d]

NS, not significant. A Poisson regression analysis was run comparing treatment groups adjusted for gender, age, diabetes, and baseline values of albumin, nPNA, and QOL (as measured by PCS, MCS, and KDCS scores).

[a] Adjusted for PCS and MCS as these two scores are approximately uncorrelated.

[b] Adjusted for KDCS independent of PCS and MCS (with which KDCS is correlated).

[c] Rate ratio.

[d] $P < 0.05$.

[e] $P < 0.01$.

[f] $P < 0.001$.

DISCUSSION

The findings of this study can be summarized as follows. Enhancement of peritoneal small solutes clearance has no beneficial effect on the evolution of quality of life in CAPD patients. Measures of quality of life have a significant predictive value for CAPD patients' survival, occurrence of hospitalizations, and their duration. HRQOL measures do not appear to influence technique survival on CAPD.

Because of the importance of the issue of dialysis dose in current nephrologic discourse [40, 44], we undertook a very detailed and rigorous evaluation of the effects of small solutes clearances on parameters of HRQOL. Both unadjusted and adjusted analysis were carried out comparing mean scores of KDQOL domains and summary scores between control and intervention groups at each follow-up of 6, 12, and 24 months. HRQOL changes from baseline to 6, 12, and 24 months of follow-up were also compared between the two groups.

In the unadjusted analysis, no long-term (12 and 24 months of follow-up) HRQOL difference was found between the two groups. At six months (short-term), a significant difference favoring the intervention group was observed in four of the KDQOL domains (burden of kidney disease, effects of kidney disease, sexual function, and

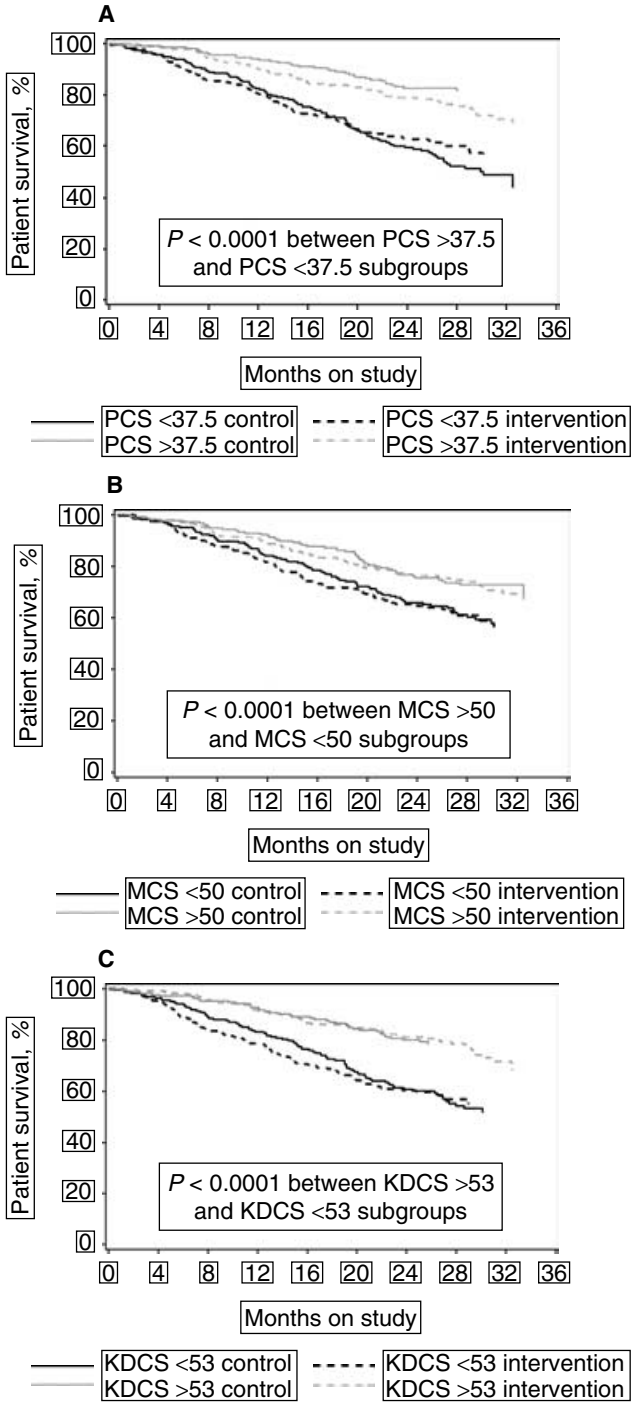

Fig. 8. (*A*) Patient survival by value of physical composite summary score (PCS) and study arm. Patients with PCS values below the mean (<37.5) had a worse survival than patients above the mean irrespective of the study arm they were randomized to. There were no differences between control and intervention in either subset of PCS. (*B*) Patient survival by value of mental composite summary score (MCS) and study arm. Patients with MCS values below the mean (<50) had a worse survival than patients above the mean irrespective of the study arm they were randomized to. There were no differences between control and intervention in either subset of MCS. (*C*) Patient survival by value of kidney disease composite summary score (KDCS) and study arm. Patients with KDCS values below the mean (<53) had a worse survival than patients above the mean irrespective of the study arm they were randomized to. There were no differences between control and intervention in either subset of KDCS.

symptom problem), while patients in the control group had a significantly higher HRQOL score in two of the KDQOL domains (cognitive function and quality of social interaction). There was also evidence of small improvement in the physical component summary score for the intervention group at six months. After adjusting for different patterns of patient dropout, however, the number of HRQOL domains showing a benefit at six months was reduced from six to four with three (effects of kidney disease, sexual function, and symptom problem) favoring the intervention group and one (quality of social interaction) favoring the control group, and no differences in the composite summary scores were found between the control and intervention groups at any time point. We have illustrated the potential bias introduced by informative censoring at length in the **Results** section of this report, and would stress the importance of giving definitive weight to the adjusted analysis in interpreting the findings of our study. Our results confirm the findings of previous smaller and uncontrolled studies in PD patients in whom dialysis dose has not been found to affect HRQOL measures [25, 34, 39].

Determinants of HRQOL in patients on peritoneal dialysis (PD) have been previously studied in small patient groups. The present study is the largest cross-sectional and longitudinal interventional study of quality of life in patients on peritoneal dialysis. Our findings confirm several of the observations done in the smaller studies regarding associations between patient characteristics and HRQOL measures such as age, gender [25], comorbidity [25, 34, 35], nutritional status [25, 35], and residual renal function [34, 35]. Many of these parameters are amenable to therapeutic interventions. While our study did not involve planned changes in these parameters, it is not unreasonable to suggest that measures to improve nutritional status, to protect residual renal function, and control the effects of comorbidities before and after the initiation of dialysis would have a salutary effect on patient HRQOL. Additionally, women with ESRD may be more vulnerable to have lower HRQOL and, hence, may need to be targeted for special care.

It is of interest to compare the baseline HRQOL measures in this large population of patients on PD and the findings in dialysis patients reported by others. Figures 9A to C compare corresponding HRQOL summary scores and specific domains in ADEMEX and the large HD population studied in the DOPPS initiative [23]. The figures illustrate that in the majority of measures, the scores in the ADEMEX population equal or exceed those in HD patients in DOPPS.

Baseline values of HRQOL in this study were highly predictive of subsequent patient survival, with lower HRQOL associated with higher mortality. This observation is similar to findings in both patients on HD and patients on PD. In patients on HD, measures of HRQOL

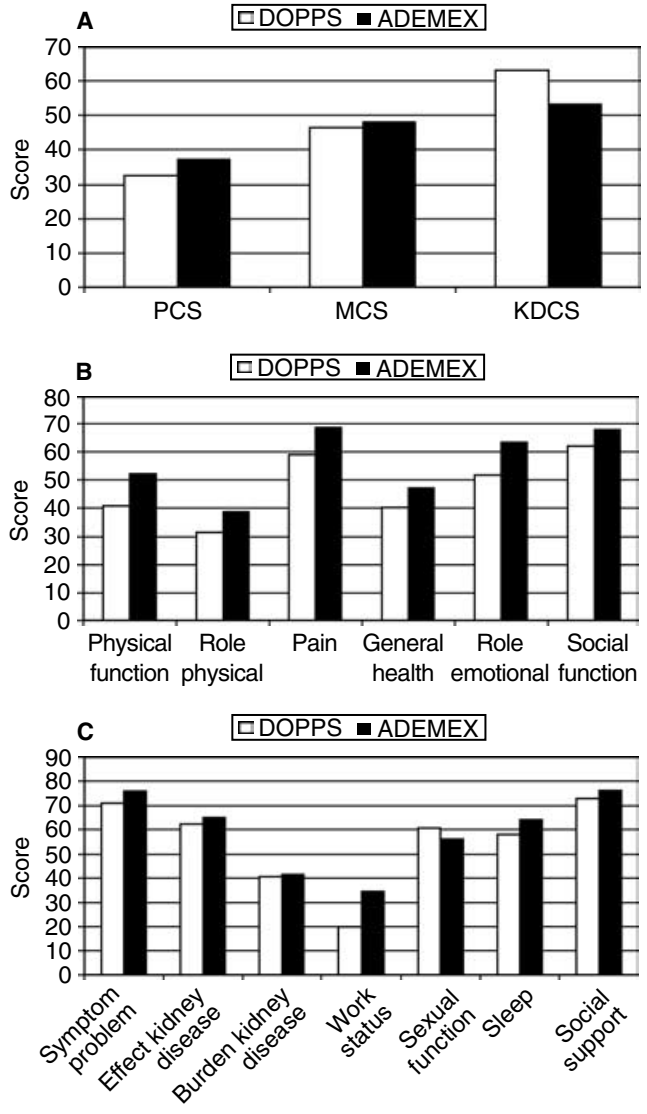

Fig. 9. (*A*) Composite summary scores in patients on peritoneal dialysis (PD) (ADEMEX) and patients on hemodialysis (DOPPS), the latter data from ref [23]. (*B*) SF-36 domain scores in patients on PD (ADEMEX) and patients on hemodialysis (DOPPS), the latter data from ref [23]. (*C*) Disease-specific domain scores in patients on PD (ADEMEX) and patients on hemodialysis (DOPPS), the latter data from ref [23].

have been found to be strong independent predictors of hospitalization and increased risk of death [16, 23, 24, 37, 56–58]. Mapes et al [23], reporting on the largest cross-sectional study in HD, showed highly significant associations between lower HRQOL scores and higher risk of death and hospitalization among hemodialysis patients. These inverse associations between HRQOL and outcomes were observed for all three components of the KDQOL-SF (i.e., MCS, PCS, and KDCS) [23]. These associations remained statistically significant after adjustment for several risk factors of death or hospitalization, including serum albumin concentration, sociodemographic characteristics, years on dialysis, type of vascular access, several comorbidities, and treatment factors [23].

Previous studies in patients on PD have also shown measures of HRQOL to be strong independent predictors of increased risk of death and hospitalizations [25, 37]. Merkus et al [37] studied prospectively a cohort of 189 patients, and found that baseline presence of comorbidity, serum albumin level of 30 g/L or less, physical or mental quality-of-life score 2 or more standard deviations less than the general population mean score, and, to a lesser extent, residual glomerular filtration rate of 2.5 mL/min/1.73m^2 or less were independently associated with a greater risk for poor outcome. Bakewell et al [25] found in 88 patients in the UK a strong correlation between poor QOL and increased rate of hospitalization. In the present study, similar to the findings of Mapes et al [23] in patients on HD, we found associations between all three composite scores of HRQOL (PCS, MCS, KDCS) and the relative risk of death. These associations remained statistically significant even after adjustments for age, presence of diabetes, baseline serum albumin, and baseline nPNA (Table 5), each of which was associated independently with risk of death. We also observed in a manner analogous to the findings of DeOreo [56] in patients on HD, that PD patients with composite scores (PCS, MCS, or KDCS) below the median had a worse survival than patients with composite scores above the median (Fig. 8A-C), independent of the dose of dialysis.

Similar to the findings of Mapes et al [23] in HD also, we observed strong associations between all three composite scores of HRQOL (PCS, MCS, KDCS) and the rate of hospitalization and the number of hospitalization days. These associations remained statistically significant even after adjustments for age, presence of diabetes, baseline serum albumin, and baseline nPNA (Tables 4 and 5), each of which was associated independently with hospitalization.

In the primary outcome report from the ADEMEX study [45], we showed that deliberate increase in peritoneal small solute clearance had no effect on patient survival. We stressed in that report that the failure to show a beneficial effect on survival in large patient cohorts does not imply that the welfare of individual patients may not be better served by enhancing the dose of dialysis [45]. We have also stressed elsewhere [44] that measures of small solute clearances alone can be uninformative, and that they need to be considered in the context of the overall care of the patient, in general, and the needs of metabolic correction in particular [44]. These earlier remarks were directed at avoiding therapeutic nihilism that may arise from a misinterpretation of our findings. These deliberations are crucial to reinvoke in the present context because of our findings of a neutral effect of enhanced small solute clearance on HRQOL. Our present report has identified areas of vulnerability in patients'

profile that may help guide future care. Women and patients with suboptimal nutritional status may need to be targeted for special care. Further, measures to protect residual renal and comorbidities effects may be translated into improved HRQOL.

CONCLUSION

ADEMEX is the first large randomized, prospective, controlled clinical trial that examined the correlates of HRQOL in patients on CAPD and the effects of peritoneal small solute clearance on patient HRQOL. Based on this randomized controlled trial, there is no evidence of a long-term benefit in HRQOL by increasing peritoneal small-solute clearances when aggregated physical, mental, and kidney disease component summary scores were used in combination with analyses that adjust for patient dropout. These results reinforce the need to adjust for possible biased censoring due to patient dropout when estimating and comparing QOL over time. Measures of HRQOL have a significant predictive value for CAPD patients' survival, occurrence of hospitalizations, and their duration.

APPENDIX

The following institutions and investigators participated in the study. Steering committee: Ramon Paniagua, MD, Dante Amato, MD, Ricardo Correa-Rotter, MD, Alfonso Ramos, MD, Edward Vonesh, PhD, John Moran, MD, and Salim Mujais, MD; Safety committee: Ramón Paniagua, MD, Dante Amato, MD, Aurora Maravilla, MD, Ma. de Jesús Ventura; Coordination and data management: Ramon Paniagua, MD, Dante Amato, MD, Ma. de Jesús Ventura, Alejandro B. Hinojosa-Rojas; Clinical monitors: Ma. de Jesús Ventura, Olga Lozano, Clara Madonia, Silvia Garnica Salazar, Inés Vaquera-Rodríguez; Central laboratory: Ramón Paniagua, MD, Ernesto Rodríguez, Marcela Ávila-Díaz, Raquel Becerril-Becerril; Advisory committee: Peter G. Blake, MD, John M. Burkart, MD, Bengt Lindholm, MD, Karl D. Nolph, MD, Robert E. Wolfe, PhD; Managing committee: Laura Trujillo, Magdalena Nemer, Angel Rodriguez; and participating centers and investigators: Ricardo Correa-Rotter, MD, Mario Cortés-Pérez, Eduardo Quintana-Piña, Josefina Loredo-Alonso, Yolanda Martínez-Cerca (Department of Nephrology and Mineral Metabolism, Instituto Nacional de Ciencias Médicas y Nutrición "Salvador Zubirán," Mexico City); Imelda Hernández-Reyes, MD, Ma. Estela Zepeda-Covarrubias (Hospital General N° 89, IMSS, Guadalajara, Jalisco); Enrique Hernández-Maldonado, MD, Magaly Cevallos-Fernández (Hospital de Especialidades, Centro Médico Nacional Ignacio García Téllez, IMSS, Mérida, Yucatán); Marcos Martínez-García, MD, Alicia Herrera-Molina (Hospital General N° 11, IMSS, Jalapa, Veracruz); Guillermo Valadez-Juvera, MD, Alma Leticia Valenzuela (Hospital de Especialidades N° 1, Centro Médico Nacional del Noroeste, IMSS, Ciudad Obregón, Sonora); José Alejandro García-Larumbe, MD, Bertha Espinoza-Pérez (Hospital General N° 30, IMSS, Mexicali, Baja California); José Luis Medina-Gómez, MD, Celestina Jiménez-Ronquillo (Hospital de Especialidades, Centro Médico Nacional Manuel Avila Camacho, IMSS, Puebla, Puebla); Eduardo Aguilar, MD, Javier Ortiz, Elizabeth Almanza-Medina (Hospital General N° 1, IMSS, Zacatecas, Zacatecas); José Martínez-Bárcenas, MD, Eloisa López-Pinales (Hospital General N° 33, IMSS, Monterrey, Nuevo León); Ma. Elena Hurtado-González, MD, Guadalupe Alcántara-Ortega (Hospital General N° 25, IMSS, Mexico City); Alejandra Cisneros-García, MD, Juan Guillermo Oros, MD, Josefina Luna-Tapia (Hospital General N° 27, IMSS, Mexico City); Jorge Prieto-Fierro, MD, Leonor Abularach-Nevares (Hospital de Especialidades, Centro Médico Nacional, IMSS, Torreón, Coahuila); Abraham Sanjurjo-Gallardo, MD, Dolores Gómez-Noriega, MD, Ma. de Lourdes Barrón-Andrade (Hospital General N° 32, IMSS, Mexico City); Mario Enríquez-Rivas, MD, Ma. Jesús Galaz-Valdez (Hospital General N° 2, IMSS, Hermosillo, Sonora); Cristina Avilés-Hernández, MD, Ma. de la Cruz Pérez-Hernández (Hospital de Especialidades, Centro Médico Nacional la Raza, IMSS, Mexico City); Gerardo Rodríguez del Villar, MD, Ma. Elena Ríos-Estrada (Hospital General N° 1, IMSS, Durango, Durango); Roberto Baca-Baca, MD, Ma. Graciela Pacheco-Hernández (Hospital General N° 1, IMSS, Querétaro, Querétaro); Ma. Juana Sil-Acosta, MD, Ma. Teresa Galindo-Salinas (Hospital General N°1 "Gabriel Mancera," IMSS, Mexico City); José Amado Chimalpopoca, MD, Ma. Isabel González-Yañez (Hospital General N° 8, IMSS, Mexico City); Francisco Belio-Caro, MD, Olivia Figueroa-Rosas (Hospital General N° 1, IMSS, Morelia, Michoacán); Julio Kaji-Kiyono, MD, Lucía Isabel Aranda-Contreras, Virginia Becerril-Morales [Hospital General Regional "1° de Octubre," Instituto de Seguridad y Servicios Sociales de los Trabajadores del Estado (ISSSTE), Mexico City]; Hugo Breien-Alcaraz, MD, Ana Gabriela Ruelas-Peralta (Hospital General "Valentín Gómez Farías," ISSSTE, Guadalajara, Jalisco); Juan Alberto Aguilar-Martínez, MD, Leticia Martínez-Guzmán (Hospital General "Gaudencio González Garza," Centro Médico Nacional la Raza, IMSS, Mexico City); Francisco Monteón, MD, José Luis Camarena, MD, Alma Rosa Martínez (Hospital de Especialidades, Centro Médico Nacional de Occidente, IMSS, Guadalajara, Jalisco).

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